A Chromatin Context Tool for Predicting iPS Lineage Predisposition and Tissue Graftability

Grant Award Details

A Chromatin Context Tool for Predicting iPS Lineage Predisposition and Tissue Graftability

Grant Type: Tools and Technologies III

Grant Number: RT3-07796

Project Objective: To test a hypothesis that a specific chromatin conformation governing TP63 activity can be used to determine the propensity of a given iPSC line to differentiate into keratinocytes for therapeutic applications.

Investigator:

Name:	Anthony Oro
Institution:	Stanford University
Type:	PI

,

Name:	Marius Wernig
Institution:	Stanford University
Type:	Co-PI

Disease Focus: Skin Disease

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,391,125

Status: Active

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: A Chromatin Context Tool for Predicting iPS Lineage Predisposition and Tissue Graftability

Public Abstract: Induced pluripotent stem (iPS) cells are cells derived from skin that closely resemble embryonic stem (ES) cells and can be coaxed into many different types of cells such as nerve cells, heart cells, liver cells, and also back to skin cells. One major bottleneck in the field is our ability to coax the cells into sufficiently pure and mature cell populations. One recognized reason for this difficulty is that every individual iPS cell line behaves slightly differently and the protocols optimized and refined to work well in one particular line do not work as well for another iPS cell line. Since robust differentiation protocols are needed for generating transplantation tissues, this line-to-line variability represents a major stumbling block for the realization of such a therapeutic approach. We here propose to develop a tool, to prospectively identify lines that will work well in a given differentiation protocol. Specifically we will develop a prediction tool whether a given iPS cell line will be able to efficiently give rise to skin cells. The tool is based on the observation that critical lineage-determination factor that regulate genes need to access the proper target sequences and that these gene sites require a permissive epigenetic configuration to be properly accessed. Validation of the approach for skin will make the tool usable in principle for predicting the differentiation of iPS cells into other medically important tissues.

Statement of Benefit to California: Cell transplantation-based therapies are heralded as new treatment options with often curative aspirations for many different kind of diseases. In particular, induced pluripotent stem (iPS) cells are intriguing potential donor cells because they can be derived from individual patients circumventing transplant rejection, and they can theoretically be differentiated into an unlimited numbers of specialized donor cells. A major hurdle limiting their usefulness is the observation that iPS cell lines are heterogeneous and that iPS cell lines from the same patient behave differently when scientists attempt to differentiate them into one particular tissue. Our chromatin context tool will provide a solution to this problem as it seeks to predict which iPS cell line will be useable for efficient differentiation. The tool is based on the observation that critical lineage-determination factor that regulate genes need to access the proper target sequences and that these gene sites require a permissive epigenetic configuration to be properly accessed. Successful development of the tool will eliminate many weeks of costly trial and error and help prospectively identify those lines that can be used for therapy. Therefore, our tool will close a critical gap that hinders clinical application of these exciting new cell-based therapies and therefore will benefit all Californians that suffer from a disease that could be treated with iPS cell-based transplantation.